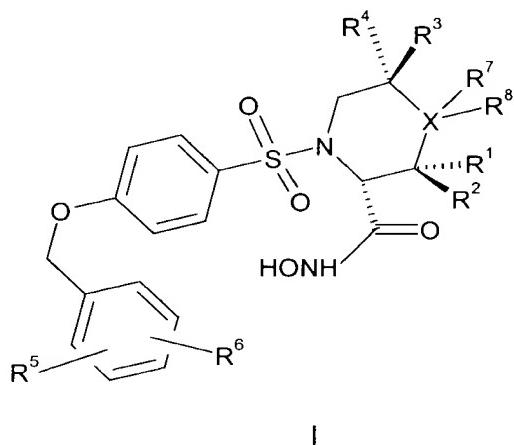


SELECTIVE INHIBITION OF AGGRECANASE IN OSTEOARTHRITIS TREATMENTAbstract

This invention relates to a method of treatment for osteoarthritis involving inhibitors of aggrecanase that demonstrate IC<sub>50</sub>s of less than 20 nM and demonstrate differential potency 5 against matrix metalloproteinases (MMPs) and a disintegrin and metalloproteinases (ADAMs or reproxlyns). This invention also relates to compounds, methods of treatment and composition of Formula I:



or a therapeutically acceptable salt thereof, wherein

10 X is carbon or nitrogen;

R<sup>1</sup> and R<sup>2</sup> are independently selected from the group consisting of hydrogen, hydroxy, and methyl, wherein at least one of R<sup>1</sup> and R<sup>2</sup> is methyl;

R<sup>3</sup> and R<sup>4</sup> are independently selected from the group consisting of hydrogen, hydroxy, and methyl, or R<sup>3</sup> and R<sup>4</sup> may be taken together to form a carbonyl group; and

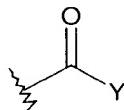
15 R<sup>5</sup> and R<sup>6</sup> are independent substituents in the ortho, meta, or para positions and are independently selected from the group consisting of hydrogen, halogen, cyano, methyl, and ethyl;

with the provisos:

when X is carbon, then R<sup>7</sup> and R<sup>8</sup> are both hydrogen and at least one of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup> is hydroxy;

when X is carbon and R<sup>5</sup> is para-halo, then at least one of R<sup>6</sup>, R<sup>3</sup>, and R<sup>4</sup> is not hydrogen;

when X is nitrogen, then R<sup>8</sup> is not present and R<sup>7</sup> is hydrogen or a group of the formula:



wherein, Y is -CH<sub>2</sub>-NH<sub>2</sub> or -NH-CH<sub>3</sub>; and  
when X is nitrogen and R<sup>7</sup> is H, then R<sup>3</sup> and R<sup>4</sup> are taken together to form a carbonyl group.